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The International Bureau of WIPO
34, chemin des Colombette
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Prague, October 12, 2005

Re: International Application No. PCT/CZ2005/000019
Applicants: I.Q.A., a.s. et al
International filing date: 15 February 2005 (15. 02. 2005)
Priority date: 20 February 2004 (20.02.2005)
Title: "STABLE, PALATABLE SYRUP CONTAINING IBUPROFEN AND METHOD OF ITS PREPARATION"
Our Ref.: P1027PC00

Informal Comments on the Written Opinion of the International Searching Authority

Dear Sirs:

In response to the Written Opinion of the International Searching Authority dated June 6, 2005, concerning the above-identified International Patent Application, we wish to submit the following comments on an informal basis.

In the reasoned statement under Rule 43bis(a) (i) with regard to novelty, inventive step or industrial applicability supported by the documents D1: EP-A-0 490 193 and D2: US-A-5 024 997 there were stated some objections to the inventive step of the present application.

In view of aforesaid we are submitting the following informal comments.

The object of the above identified application is stable palatable syrup containing S(+)-ibuprofen and method of its preparation. The syrup of the present invention according to claim 1 contains S(+)-ibuprofen, hydroxypropyl beta-cyclodextrin, sweetener, water and optionally essential oils in defined amounts.

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The cited document D1, relating to S(+)-ibuprofen - beta-cyclodextrin complexes, discloses that the S(+)-ibuprofen - beta-cyclodextrin complexes have enhanced solubility and bioavailability of S(+)-ibuprofen and therefore are suitable for use in preparation of a syrup containing S(+)-ibuprofen.

To the objection that the subject-matter of claim 1 of the present application differs from that of D1 only in specifying the presence of sweetener we wish to point out that the subject-matter of claim 1 of the present application differs from that of D1in more aspects than only in specifying the presence of sweetener. In D1, a complex of S(+)-ibuprofen with cyclodextrin, prepared by phase-transformation technique, is used for the preparation of the syrup. During the phase transformation the S(+)-ibuprofen is melted in aqueous suspension of suitable cyclodextrin as a host molecule and after exceeding its melting point a solid crystalline complex is formed. As stated the crystalline complex is more soluble than the non-complexed S(+)-ibuprofen and also the undesired bitter taste of ibuprofen is reduced - these properties being favourable for use in pharmaceutical preparations.

Example 10 of D1 teaches the use of the solid crystalline complex for the preparation of the syrup containing S(+)-ibuprofen. As cyclodextrin derivative there was in this example used 2,6-di-O-methyl-beta-cyclodextrin. The cyclodextrin derivative used in the present application, hydroxypropyl beta-cyclodextrin, is mentioned only in claims 11 and 18 of D1 as one of the cyclodextrin derivatives possibly suitable for the preparation of the S(+)-ibuprofen-containing solid crystalline complex and its use for the preparation of the syrup is not disclosed in D1. The weight ratio of S(+)-ibuprofen to cyclodextrin derivative in the syrup of example 10 of D1 is 1:6.47. This ratio cannot be used for the preparation of the syrup of the present invention, i.e. using the S(+)-ibuprofen solution instead of the solid crystalline complex of S(+)-ibuprofen and cyclodextrin. Long-term stability and masking of the unpleasant taste can be reached in the liquid pharmaceutical preparations containing the non-complexed S(+)-ibuprofen only at the weight ratio of S(+)-ibuprofen and cyclodextrin of from 1:11 to 1:18. At lower weight ratios the S(+)-ibuprofen is not dissolved totally and the taste-masking is incomplete.

According to D1, the complex of S(+)-ibuprofen and cyclodextrin derivative is prepared at a temperature of 60 °C yielding a solid substance composed of both components, which is subsequently dissolved for the preparation of the syrup. In the present application, the S(+)-ibuprofen is dissolved in aqueous solution of hydroxypropyl beta-cyclodextrin at a temperature lower than the melting point of S(+)-ibuprofen, i.e. at a temperature ranging from 40 to 45 °C. At higher temperatures, taught for the preparation of the complex in D1, the pharmaceutical preparation yielded has insufficient long-term stability and incomplete masking of the unpleasant taste.

The pharmaceutical preparation claimed in the present application differs from the pharmaceutical preparations of D1 in the following aspects:

- use of the solutions of S(+)-ibuprofen and hydroxypropyl beta-cyclodextrin instead of the complex of S(+)-ibuprofen and different cyclodextrin derivative in solid form;
- the processing temperature not exceeding 50 °C, preferably ranging from 40 to 45 °C, instead of 60 °C necessary for the preparation of the complex of D1;
- the cyclodextrin derivative used for the preparation of the syrup;
- the weight ratio of S(+)-ibuprofen to hydroxypropyl beta-cyclodextrin, which substantially differs from that of S(+)-ibuprofen to 2,6-di-O-methyl betacyclodextrin in the complex used for the preparation of the syrup of D1.

It follows from the above listed arguments that the subject-matter of the present invention is not obvious for a person skilled in the art and it involves an inventive step over D1.

The subject-matter of the present application differs also from that of the cited document D2. S(+)-ibuprofen has different physical properties compared to the racemic form of ibuprofen. It shows different behaviour when being dissolved in common solvents, has a substantially lower melting point (50 to 54 °C) compared to the racemate (75 to 78 °C) and under neutral and basic conditions the racemization of S(+)-ibuprofen occurs. For these reasons the processes used for the racemic ibuprofen are not directly transferable to the preparation of pharmaceutical preparations containing the S(+)-ibuprofen. The composition and conditions suitable for the preparation of long-term stable pharmaceutical preparations containing racemic ibuprofen do not provide in case of S(+)-ibuprofen stable products, but products in which a micro-emulsion of S(+)-ibuprofen is formed and the racemization occurs.

The document D2 teaches the preparation of syrup containing racemic ibuprofen, in which the ibuprofen is dissolved in aqueous solution of hydroxypropyl beta-cyclodextrin at 50 °C; and in example 5 of D2 the solution of racemic ibuprofen and cyclodextrin is added to further components even at a temperature of 60 °C. When using the S(+)-ibuprofen under the same conditions there occurred in the course of dissolution and stirring its melting under the formation of a suspension which was long-term unstable, physically unstable and entirely unsuitable for pharmaceutical preparations. Furthermore, the attempts to mask the unpleasant taste of the S(+)-ibuprofen in the pharmaceutical preparation prepared under such conditions were not successful. Surprisingly, the inventors of the present invention have found that by working-up the mixture at lower temperature such undesirable effects can be avoided. Therefore, in the present application the S(+)-ibuprofen is dissolved at the temperature range of from 15 to 50 °C, preferably from 40 to 45 °C, at which the undesirable effects do not occur.

The contents of the S(+)-ibuprofen in the syrup of the present invention is also lower than in the syrup according to D2 (0,01-2 % w/v in contrast to 2-5 % w/v). The same applies even if the enhanced activity of the S(+)-isomer in comparison with the racemate is taken into consideration.

The subject-matter of the present application, which is stable palatable syrup containing S(+)-ibuprofen and its preparation, cannot for the above indicated reasons be reached by simply using S(+)-ibuprofen instead of racemic ibuprofen under the conditions taught in D2, neither by using the active substance of D1(the complex of S(+)-ibuprofen with 2,6-di-O-methylbetacyclodextrin) under the conditions taught in D2. The present solution is not obvious for a person skilled in the art from the combination of D1 and D2. Therefore, the independent claim 1, the claims dependent on claim 1 and the claims concerning the method of preparation of the syrup, in our opinion involve an inventive step over D1 and D2.

Respectfully submitted,

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Agent for Applicant